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# Dosage regimen evaluation of antiretroviral gold nanoparticles using Monte Carlo Simulation

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## OBJECTIVE

**Evaluation of a dosage regimen of antiretroviral gold nanoparticles (GNP) based on the PK/PD parameters estimated by Monte Carlo Simulation, to improve the efficacy into the reservoir (macrophages).**

## METHODS

An improved PK/PD model of antiretroviral gold nanoparticles previously developed has been used[1]

**** PK/PD Model***

**Pharmacokinetic model (PK)**

$$\frac{dC_{GNP}(t)}{dt} = D * e^{-(Ke)*t}$$

$$\frac{dC_{drug}(t)}{dt} = Krel * C_{GNP} * -Ke_{intraCell} * C_{drug}$$

**Inhibition model**

$$INH = (I_{max} * \ C^{\gamma}\ )/(IC_{50}{}^{\gamma} + C^{\gamma}\ )$$

**Pharmacodynamic model (PD)**

$$\frac{dCell(t)}{dt} = Cell\ load - (InfectionCapacity*(1-INH))$$

$$\frac{dV(t)}{dt} = Virions\ load - Ke * V$$

**PK/PD Parameters**

Values from literature[2-6]
(CV= 20% )

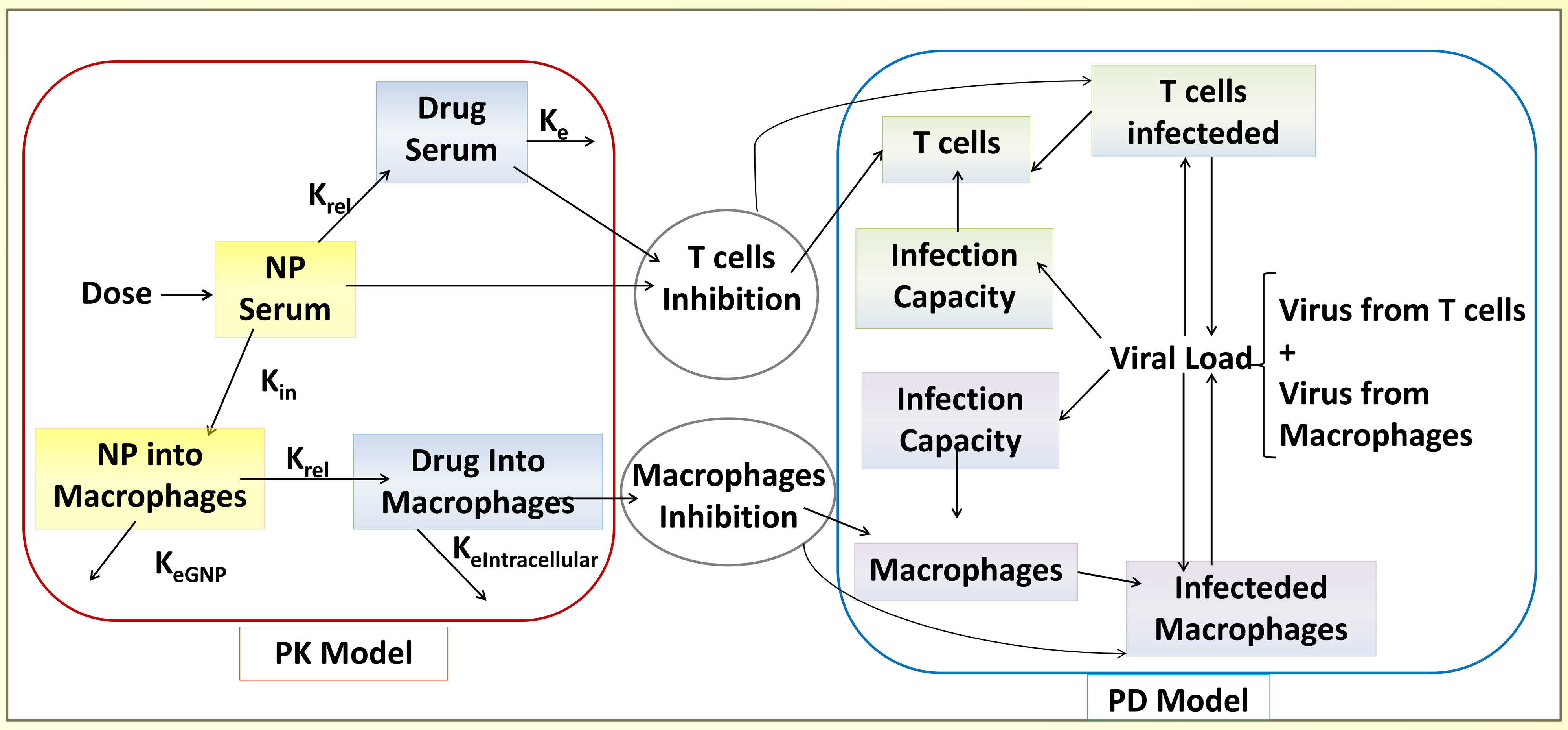


**Fig 1.** Antiretroviral gold nanoparticles PK/PD model

**** Monte Carlo Simulation***

10,000 HIV individual patients
10 years of treatment
Software: GoldSim

**** IV Dosage Regimens***

They were designed taking into account:
- toxic gold nanoparticles (GNP) concentration
- serum and inside cell stavudine concentrations achieved with conventional formulation (40 mg/12 h)

## RESULTS

**Table 1.** GNP and stavudine maximum serum concentrations by Monte Carlo Simulation

| Dosage Regimen | Mean $C_{maxGNP}$ serum (mM) | Mean $C_{maxDrug}$ serum (mg/L) | Mean $C_{maxDrug}$ Inside cell (mg/L) |
|---|---|---|---|
| 1 mg/kg/day | 0.07 | 0.19 | 0.50 |
| 2 mg/kg/day | 0.12 | 0.44 | 1.16 |
| 2 mg/kg/2days | 0.12 | 0.22 | 0.93 |
| 4 mg/kg/2days | 0.24 | 0.96 | 2.27 |
| 3 mg/kg/3days | 0.17 | 0.70 | 1.49 |
| 6 mg/kg/3days | 0.36 | 1.48 | 3.31 |
| Toxic Value | 0.50 | - | - |
| Conventional treatment | - | 0.70 | 0.34 |

**Table 2.** Probability of exceeding (PE) and not exceeding (PnotE) Viral load and T cells target values after 6 years of treatment, by Monte Carlo Simulation

| Dosage Regimen | PnotE Total Viral Load (<100 virions/uL) | PnotE Macrophages Viral Load (<10 virions/uL) | PE T cells number (>4 $10^6$ T cells/uL ) |
|---|---|---|---|
| 1 mg/kg/day | 0.66 | 0.46 | 0.52 |
| 2 mg/kg/day | 0.73 | 0.58 | 0.73 |
| 2 mg/kg/2days | 0.64 | 0.42 | 0.35 |
| 4 mg/kg/2days | 0.65 | 0.44 | 0.38 |
| 3 mg/kg/3days | 0.54 | 0.38 | 0.25 |
| 6 mg/kg/3days | 0.55 | 0.40 | 0.28 |
| Conventional treatment | 0.00 | 0.00 | 0.00 |

Simulations show:
- GNP serum concentration lower than toxic one.
- Drug concentration inside the cell higher than with conventional treatment.
- High probability of keeping low total viral load.
- High probability of keeping low viral load from the macrophages, which is very important to avoid relapse.
- High probability of having more T cells and during more time than with the conventional treatment.

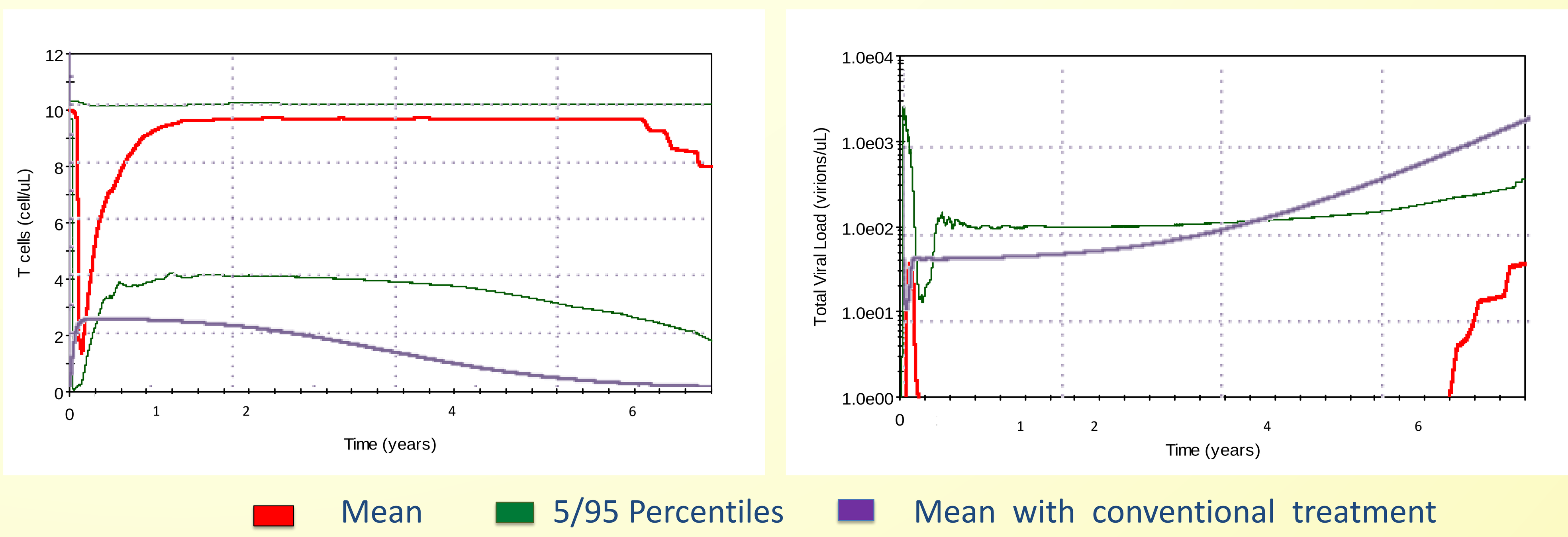


**Figure 1.** Evolution of Viral Load and T cells during 10 years of treatment with 2 mg/kg/day of antiretroviral gold nanoparticles.

## CONCLUSION

**According to the Monte Carlo simulation with the PK/PD antiretroviral gold nanoparticles model developed, the best dosage regimen evaluated is 2 mg/kg/day. This dosage regimen lets to control the viral load and the T cells number with a high probability (>70 %) during more than seven years with low drug and GNP serum concentrations.**

## REFERENCES

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